EXHIBIT B

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Classification of biomaterials and their related complications in abdominal wall hernia surgery

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Summary: The value of the use of biomaterials for the repair of abdominal wall hernias is gaining increasing recognition. The use of synthetic mesh to achieve a tension-free repair has resulted in a significant reduction in post-operative pain, in length of the recovery period, and in the number of recurrences. However, certain physical properties of biomaterials can lead to undesirable consequences. These include increased risk of infection, seroma formation, biomaterial-related intestinal obstruction, and fistula formation and failure of repair due to shrinkage of the mesh. The purpose of this paper is to discuss the mechanism of these problems with special emphasis on pore size, molecular permeation and shrinkage of biomaterials and their effects on infection, seroma formation, and recurrence of mesh repair of abdominal wall hernias.

Key words: Biomaterials — Mesh — Mesh plug — Tension-free repair — Mesh complications

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In the early 1800s, the degenerative nature of inguinal hernia was suspected by Cooper. In the latter part of that century, Billroth realized the need for prosthetic reinforcement of the inguinal floor, musing that, if only the proper material could be created to "....artificially produce tissue of density and toughness of fascia and tendon, the secret of the radical cure of hernia would be discovered".

In 1959, Billroth's dream was realized when polyethylene mesh was introduced by Francis Usher. In the decades since, there has been a transition to polypropylene, and the introduction of additional synthetic materials. While from the chemical point of view, all these synthetics are completely biocompatible, some physical and structural properties of the prostheses are associated with certain complications. However, these complications are entirely preventable if their causes are recognized in advance and accounted for.

Prevention of biomaterial-related complications requires in-depth knowledge and understanding of the physical properties of prostheses, of which, the porosity and the pore size of the materials are of paramount importance. Classification of available biomaterials for hernia surgery is essential for the everyday practical use of prostheses. Based on their pore size, the most frequently-used materials in hernia surgery can be grouped into four types:

Type I: Totally macroporous prostheses, such as Atrium, Marlex, Prolene and Trelex. These prostheses contain pores larger than 75 microns, which is the required pore size for admission of macrophages, fibroblasts (fibroplasia), blood vessels (angiogenesis) and collagen fibers into the pores [Bobyn et al. 1982, White 1988, White et al. 1981].

Type II: Totally microporous prostheses, such as expanded PTFE (Gore-

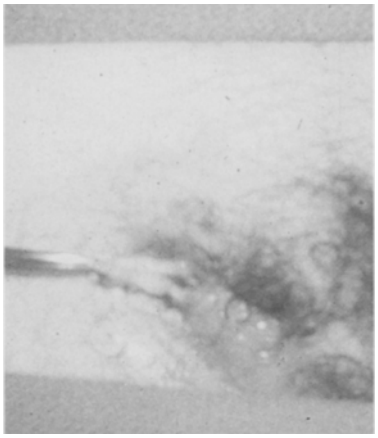


Fig. 1
Infected and partially extruded Gore-Tex soft tissue patch

Tex), Surgical Membrane, and Dualmesh. These prostheses contain pores that are less than 10 microns in at least one of their three dimensions.

Type III: Macroporous prosthesis with multifilamentous or microporous components, such as PTFE mesh (Teflon), braided Dacron mesh (Mersilene), braided polypropylene mesh (Surgipro) and perforated PTFE patch (MycroMesh).

Type IV: Biomaterials with submicronic pore size, such as silastic, Cellgard (polypropylene sheeting), Preclude Pericardial membrane and Preclude Durasubstitute. These are not suitable prostheses for hernia repair; however, in combination with Type I biomaterials, they can provide adhesion-free composites for intraperitoneal implantation [Amid et al 1995a, 1994, Amid and Lichtenstein 1996].

Biomaterial-related complications frequently encountered in hernia surgery are: infection, seroma formation, intestinal adhesion, bowel obstruction, erosion of the prostheses into the adjacent hollow viscus, and failure of the repair due to contraction of the prostheses.

Infection

Surgical infection promoted by implantation of biomaterials, such as sutures and prostheses, is caused by infiltration and proliferation of bacteria into and within the pores and interstices of these synthetic materials. When interstices or pores are less than 10 microns, in each of their three dimensions, bacteria ave-

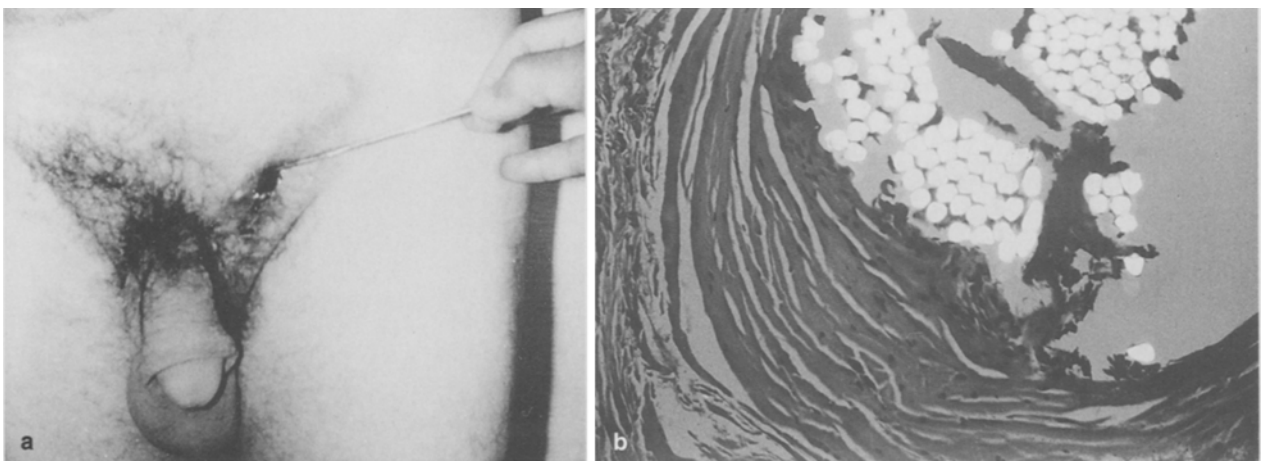


Fig. 2a, b
a Chronic infection and sinus tract formation after hernia repair with Surgipro. **b** Multifilamentous fibers of Surgipro surrounded by inflammatory cells (polarized lighting)

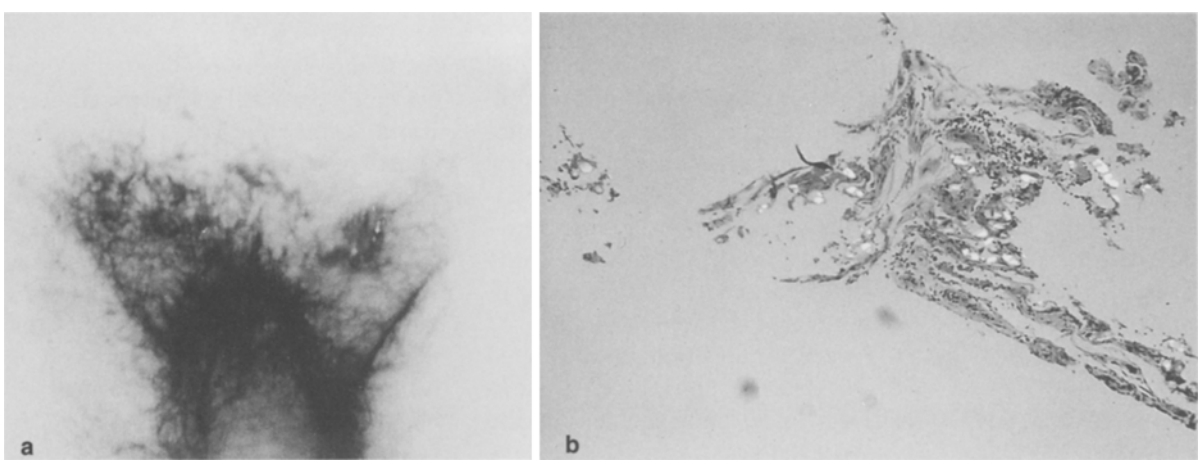


Fig. 3a, b
a Chronic infection and sinus tract formation after hernia repair with Marlex mesh, sutured in place with braided suture material. **b** Braided suture material surrounded by inflammatory cells (polarized lighting)

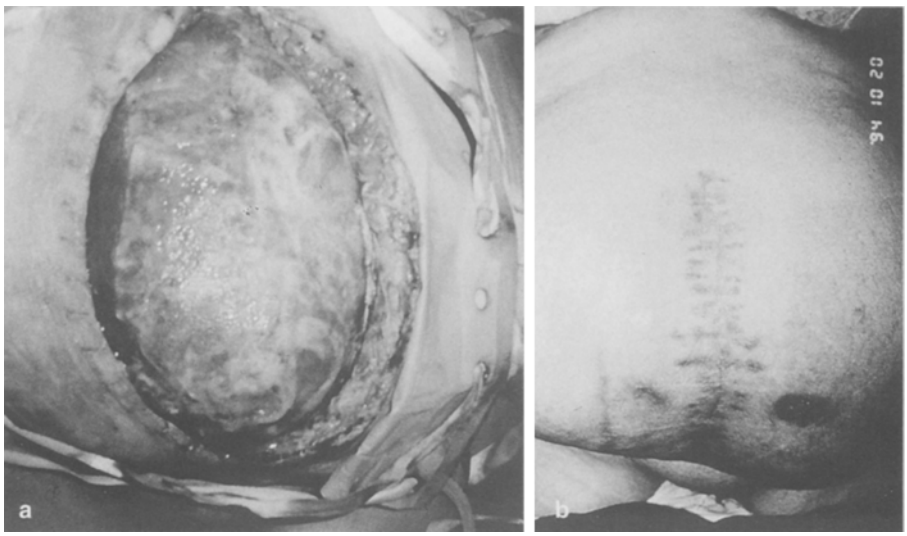
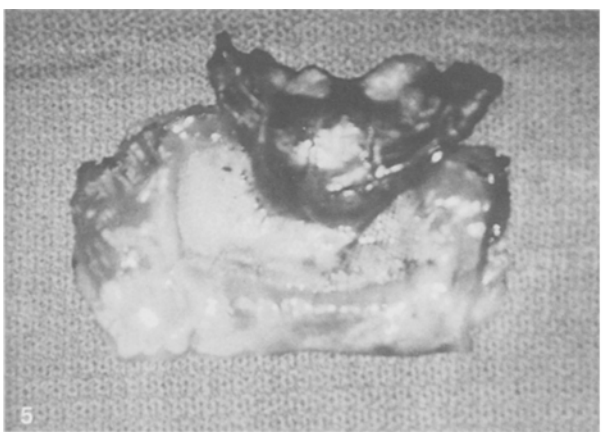


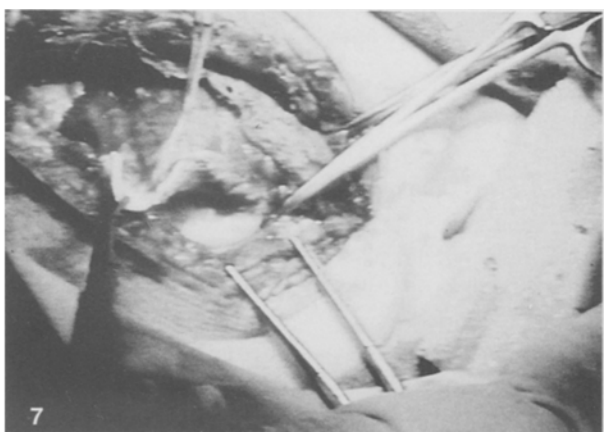
Fig. 4a, b
a Three day post-incision and drainage of a massive wound infection, following repair of a large incisional hernia. The mesh is completely covered by granulation tissue. **b** Complete healing of the wound after secondary closure without removing the mesh

raging 1 micron cannot be eliminated by macrophages and neutrophilic granulocytes, which are too large to enter a 10 microns three-dimensional pore [Alexander et al. 1967, Elek and Conen 1957, Neel 1983]. Braided sutures [Elek and Conen 1957] and prosthetic material [Neel 1983] with interstices and pores less than 10 microns provide a suitable housing for bacteria and development of infection by admitting bacteria but excluding macrophages. By admitting both macrophages and bacteria, biomaterials with pores larger than 10 microns create a major challenge for the proliferation of bacteria, and thus do not contribute to the development of surgical infection [Larson and Harrower 1978, Law and Ellis 1991, Martin et al. 1982, Usher et al. 1959].

Type II and III prostheses are similar to braided suture materials, and by harboring bacteria can promote their growth, likewise resulting in biomaterial-related infection [Alexander et al. 1967, Elek and Conen 1957]. Figure 1 is an example of an infected and partially extruded Type II prosthesis; Figure 2a and b, of an infected Type III.

Contrary to Type II and III, Type I prostheses deter housing and growth of bacteria, not only by admitting macrophages, but because they allow rapid fibroplasia and angiogenesis within their sufficiently wide pores, which also prevents infiltration and growth of bacteria [Arnaud et al. 1977, Merritt et al. 1979].





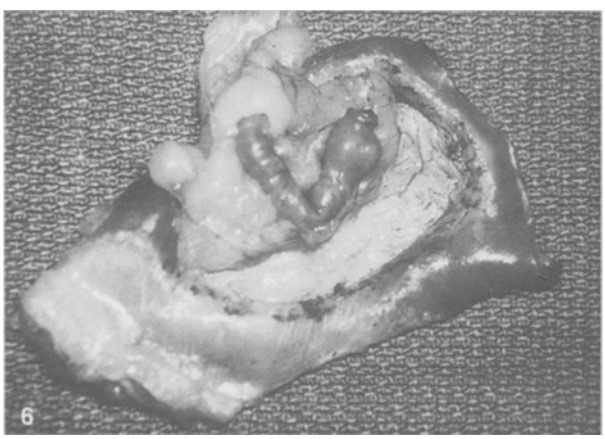


Fig. 6
Adhesion of the intestine to Vicryl mesh (rabbit model)

Fig. 5
Adhesion of the intestine to Marlex mesh (rabbit model)

Fig. 7
Adhesion of the intestine to Gore-Tex soft tissue patch (in human)

Frequently, sinus tract formation and chronic infection following Type I prosthetic repair of hernias are caused by utilization of multifilamentous suture material for the fixation of the mesh, although they are mistaken for being caused by the mesh itself [Berliner 1994, Larson and Harrower 1978, Notaras 1974]. Figure 3a and b are examples of this repeatedly confused issue.

Although infection rate associated with Type II and III prostheses is

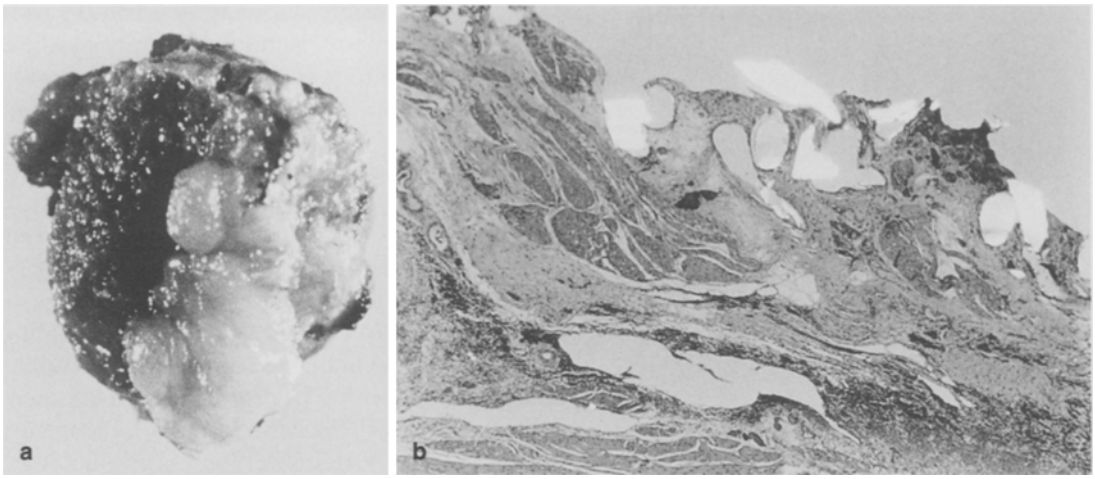


Fig. 8a, b
a Erosion of a shrunken soft Marlex plug into the bladder wall. **b** Microscopic view of the same (polarized lighting)

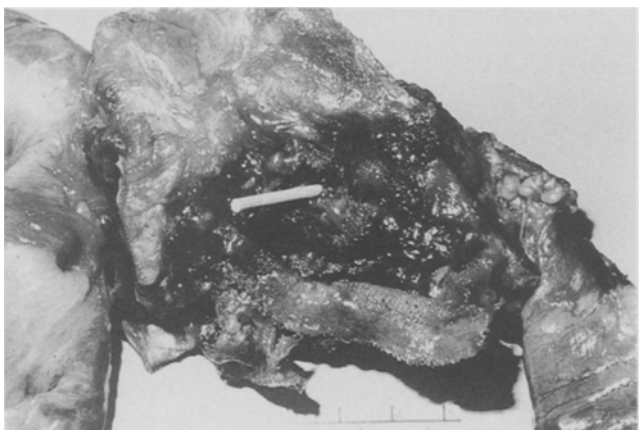


Fig. 9
Migration of Marlex mesh into the bowel (courtesy of Dr. Leon Morgenstern)

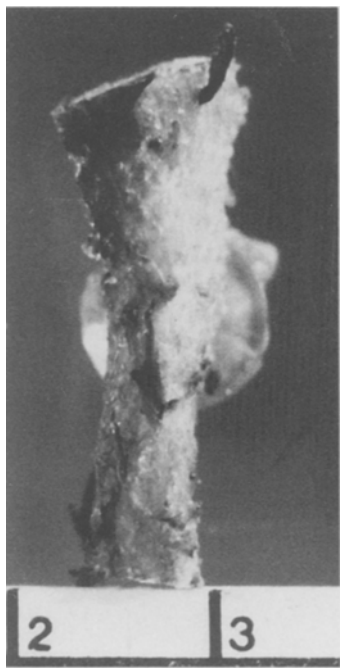


Fig. 10
Shrinkage of a soft Marlex plug, 2 cm in diameter (75% reduction in size)

within a reasonable rate, higher rates of 9.6% [DeBord and Wyffels 1992] to 50% [Smith 1971] associated with their utilization have been reported. Such numbers have not been encountered in association with Type I biomaterials.

More importantly, in connection with surgical infection from other causes, the totally macroporous protheses (Type I) do not have to be removed; drainage of the infected area, followed by local wound care, is all that is necessary to manage the infection (Fig. 4a, b) [Capozzi et al 1988, Matapurkar et al. 1991, Molloy et al 1991]. By contrast, total removal of the Type II prosthesis [Berliner 1994, DeBord et al. 1992] and at least partial removal of the Type III [Stoppa et al. 1984] is required in order to manage infection associated with their utilization.

Seroma

Postoperative prosthetic-related seroma formation is caused by host inflammatory reaction to the prosthesis (which modern biomaterials have made negligible), and by the dead space created between the prosthesis and host tissue. Adequate pore size gives Type I and III prostheses sufficient molecular permeability to allow penetration of host proteinaceous material into their pores [Arnaud et al 1977]. Since this results in a rapid fibrinous fixation of the mesh to the tissue and elimination of the dead space between the prosthesis and the host tissue, the chance of seroma formation is minimized [Amid et al. 1992]. Sufficient molecular permeability also results in formation of proper scaffolding for future host tissue incorporation [White 1988], which —by filling-up the pores of the mesh and making them inaccessible to bacteria—further decreases the chance of biomaterial-related seroma formation and infection [Arnaud et al. 1977, Merritt et al 1979].

The risk of seroma can be reduced to virtually zero by avoiding direct contact with the subcutaneous adipose tissue by retromuscular or subaponeurotic placement of the mesh [Amid et al 1995, Arnaud et al 1977, Smith 1971], and by a closed system drainage of the

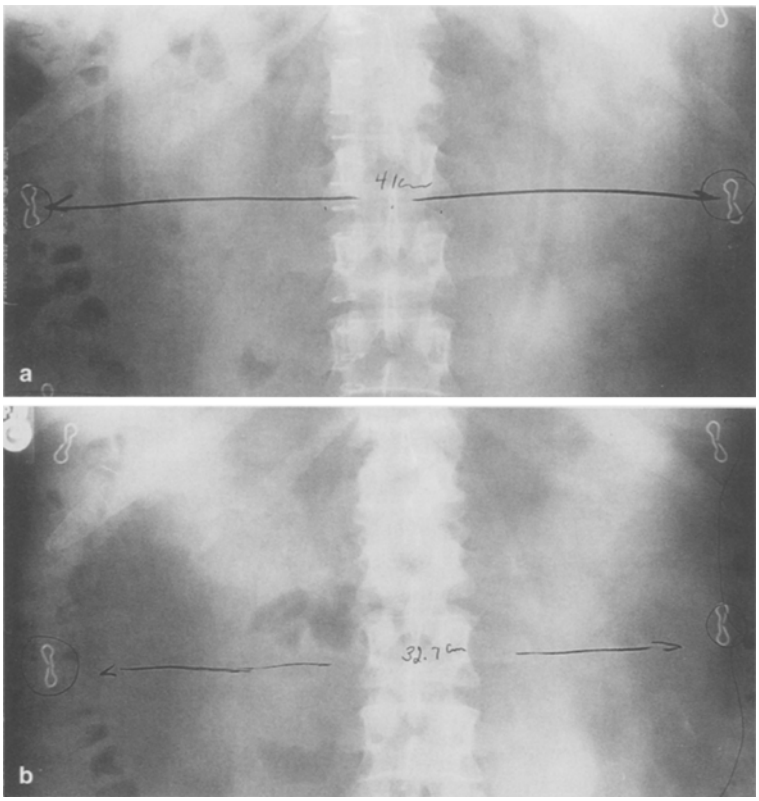


Fig. 11a, b
a Abdominal wall radiograph one day after implantation of polypropylene mesh. **b** Abdominal wall radiograph of the same patient ten months after implantation of polypropylene mesh

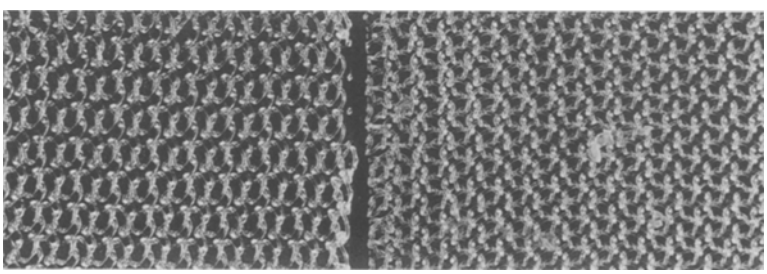


Fig. 12
Left - Marlex mesh (control). Right - Marlex mesh removed from a patient one year after its implantation

surgical field whenever a large sheet of mesh is used [Rath et al, 1996].

Because of their inadequate pore size, Type II biomaterials lack sufficient molecular permeability for the host fibrinous and proteinaceous materials, thus resulting in slow elimination of the dead space between the prosthesis and the host tissue and the formation of seroma [Amid et al. 1992].

Although the reported rate of seroma formation associated with Type II prostheses is within a reasonable range, higher rates of 14.6% in incisional hernia repair [DeBord et al 1992] and 9.6% in inguinal hernia repair [Law and Ellis 1990] have been reported. No such increased rates of seroma formation have been cited in the surgical literature in connection with properly implanted Type I and Type III prostheses.

Intestinal adhesions

The most important characteristics of ideal prostheses for abdominal wall hernia surgery are macroporosity [Bobyn et al. 1982, Molloy et al. 1991, White 1988] and surface texture [Taylor and Gibbons 1983]. These qualities combine to create the degree of host tissue infiltration into the prostheses which is critical to a strong and secure hernia repair.

However, an undesirable side effect of macroporosity is the adherence of macroporous meshes to the bowel when they come in direct contact with the intestinal tract [Amid et al. 1994, Crist and Gadasz 1993, Soler et al. 1993]. At the present time, all available prostheses (absorbable and nonabsorbable) adhere to the intestines [Amid et al. 1994, Crist and Gadasz 1993, Soler et al. 1993], (Figs. 5, 6, 7). Covering the mesh on its intestinal side with a layer of absorbable material such as Vicryl, or with expanded PTFE patch, does not solve this problem [Solar et al, 1993] (Fig. 7). Our experimental studies have shown that composites made of the combination of Type I and Type IV materials can prevent this complication, as well as the resultant bowel obstruction and intestinal fistula formation [Amid and Lichtenstein 1996, Amid et al. 1994, Amid et al. 1995].

Hollow viscus erosion and fistula formations

Another undesirable side effect of macroporous materials is erosion and migration of the prosthesis into the GI tract when they are in direct contact with the intestines. This complication is even more common when the prosthesis is in direct contact with organs without serosal covering: the distal esophagus [Schneider et al 1970], rectum [Kaufman et al 1981], bladder [Hume and Bour 1996] (Fig. 8a, b) and denuded intestinal tract. Direct contact of the prosthesis with the normal intestine covered by an intact serosal layer can also lead to fistula formation [Amid et al. 1995, Crist and Gadasz 1993, DeGuzman et al. 1995, Flament and Palot 1994, Jones and Jurkovich 1989, Seelig et al. 1995] (Fig. 9).

Experimental studies and clinical observation have shown that covering the intestinal side of the mesh with a layer of absorbable material does not

prevent erosion and migration of prostheses [Soler et al. 1993].

Contraction of the prosthesis

1. *Shrinkage of the prosthetic plug (mesh plug).* After implantation, and depending on their looseness, mesh plugs shrink up to 75%, thus failing to secure the repair. A loose or soft plug which can be collapsed by pinching it between two fingers (the pinch test) loses size during the patient's own scarring process. As a result, the anchoring sutures of the plug pull through the margin of the hernia defect, leading to recurrence of the hernia. More importantly, after scarification and shrinkage, even a soft plug assumes a cartilage-like consistency which can erode into the bladder (Fig. 8a, b).

2. *Shrinkage of the mesh patch.* Contraction of the mesh fibers during the scarring process leads to shrinkage of the mesh after implantation *in vivo*. Radiographic measurements of the distances between the metallic staples used for the preperitoneal mesh repair of incisional hernias [Amid et al. 1994b] made ten months after implantation reveal a contraction of approximately 20% (Fig. 11a, b) when compared to measurements taken shortly after the procedure.

Furthermore, comparison between mesh removed from patients and processed through an alcohol-methyl salicylate clearing sequence with that of a control demonstrates that the pore sizes of the removed mesh are approximately 20% smaller (Fig. 12).

Conclusion

Utilization of synthetic materials in abdominal wall hernia surgery has become increasingly popular. The use of synthetic mesh to achieve a tension-free repair has resulted in a significant reduction in post-operative pain, length of recovery period and the rate of post-operative recurrences. However, it must be noted that certain physical properties of biomaterials can lead to undesirable consequences, including increased risk of infection, seroma formation, biomaterial-related intestinal obstruction and fistula formation, and failure of the repair due to shrinkage of the mesh. When the mechanisms of these problems are understood and proper precautions are taken, prostheses can be used with minimal or no complications. These precautions include the following:

1. The risk of infection can be avoided by utilization of Type III and particularly Type I prostheses.

2. The risk of seroma formation can be virtually eliminated by subaponeurotic and retromuscular implantation of Type I and Type III prostheses, and drainage of the surgical field whenever a large sheet of mesh is used.

3. The possibility erosion and of mesh-related intestinal adhesion, bowel obstruction and fistula formation can be eliminated by avoiding mesh plugs and direct contact between the mesh and the intestinal tract, or utilization of adhesion-free composites.

4. Finally, problems associated with contraction of the mesh can be circumvented by using a sufficiently large piece of mesh to provide adequate mesh/tissue interface beyond the boundary of the hernia defect, and by maintaining adequate laxity of the mesh while it is being fixed to the abdominal wall tissue [Amid 1995b].

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